REC'D 0 6 JUN 2000

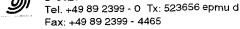
WIPO

PCT

(PCT Article 36 and Rule 70)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

Applicant's or agent's file reference		See Notification of Transmittal of International		ation of Transmittal of International			
PP/NT/PH/3281		FOR FURTHER ACT	FION Preliminary	Examination Report (Form PCT/IPEA/416)			
International application No.		International filing date (day/month/year)		Priority date (day/month/year)			
PCT/GB99/0	00968	26/03/1999		27/03/1998			
International Pa C12Q1/68	atent Classification (IPC) or na	tional classification and IPC					
Applicant							
ISIS INNOV	'ATION LIMITED et al.						
1. This inte	This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.						
2. This REI	PORT consists of a total of	8 sheets, including this	cover sheet.				
bee (see	This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of 2 sheets.						
3. This rep	ort contains indications rela	ating to the following item	ns:				
 	Basis of the report						
	☐ Priority						
	\square Non-establishment of α	opinion with regard to nov	velty, inventive step	and industrial applicability			
IV	Lack of unity of inventi						
V	 Neasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement 						
1	Certain documents cit						
ł .	VII 🛮 Certain defects in the international application						
VIII	☑ Certain observations o	on the international applic	eation				
Date of subm	ission of the demand		Date of completion o	of this report			
27/10/1000	1		02.06,2000				



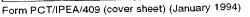
preliminary examining authority:

27/10/1999

Renggli, J

Authorized officer

Telephone No. +49 89 2399 7461



European Patent Office

Name and mailing address of the international

D-80298 Munich



INTERNATIONAL PRELIMINARY EXAMINATION REPORT



International application No. PCT/GB99/00968

I.	Ba	sis	of	the	rep	ort
----	----	-----	----	-----	-----	-----

•	pasis of the report					
1.	This report has been drawn on the basis of (substitute sheets which have been furnished to the receiving Office response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.):					
	Des	scription, pages:				
	1-12	2	as originally	filed		
	Clai	ims, No.:	-		•	
	1-14	4	with telefax of	of	25/04/2000	
2.	The	amendments have	resulted in th	ne cancel	lation of:	
		the description,	pages:			
		the claims,	Nos.:			
		the drawings,	sheets:			
3.		This report has be considered to go b	en establishe beyond the di	ed as if (so sclosure a	ome of) the amendments had not been made, since they have been as filed (Rule 70.2(c)):	
4.	Add	ditional observations	s, if necessar	y:		
V.	Rea app	asoned statement blicability; citation	under Article s and explan	e 35(2) w nations si	ith regard to novelty, inventive step or industrial upporting such statement	
1.	Sta	tement				
	Nov	velty (N)	Yes: No:	Claims Claims	1-9 10-14	
	Inve	entive step (IS)	Yes: No:	Claims Claims	1-9 10-14	
	Ind	ustrial applicability	(IA) Yes:	Claims	1-14	



INTERNATIONAL PRELIMINARY EXAMINATION REPORT



International application No. PCT/GB99/00968

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet





International application No.

INTERNATIONAL PRELIMINARY InterEXAMINATION REPORT - SEPARATE SHEET

PCT/GB99/00968

ITEM V:

- 1. Reference is made to the following documents:
- D1 ABRAMSON ET AL, PUBLIC HEALTH REVIEW, vol. 26, no. 2, February 1998, pages 127-144
- D2 DATABASE CHEMABS [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US1997 GCGA, STN Database accession no. 126:273057 & NAT. GENET. (1997), 15(4), 389-392, 1997
- D3 DANIELS ET AL, NATURE, vol. 383, 1996, pages 247-50
- D4 Asthma Gene Database, server http://cooke.csf.de/asthmagen/db/show.clm Main Tables, chr. 2, linkage table p < 0.5, cited by the applicant
- 2. Industrial applicability (Art. 33(4) PCT):

The subject-matter of claims 1-14 is susceptible of industrial application.

3. Novelty (Art. 33(2) PCT):

D1 reviews the state of the art of asthma related genetic markers and summarizes the results obtained in D2 and D3. The following regions of interest have been exemplified in D1 and D2 or D1 and D3: chromosomes 2q33, 4, 5p15, 6, 7, 11p15, 13, 16, 17p11.1-q11.2, 19q13 and 21q21 (see D1, abstract and page 137, last paragraph, Table 2; see D2, abstract and D3, tables 1 and 2). Only D1 and D2 disclose a asthma-related chromosome 2 region.

The region 2q33 which is associated with asthma as shown in D1 and D2 would appear to be different from the region claimed in claim 1 of the present application, since the D1/D2 regions listed in document D4 under the heading Collaborative 1997 are all located on chromosome 2 at a distance superior to 1 Mb/cM from the locus D2S308.

The subject-matter of claim 1 is therefore novel over D1/D2. It follows that claims 2-9





International application No. PCT/GB99/00968

meet the requirements for novelty.

Concerning claims 10-14, it should be noted that the unclear definition of the sequences, i.e. by the result to be achieved or using the wording "substantially similar sequences" (see section VIII, below), does not make the intended limitations clear. Since the sequences claimed are not clearly defined, the objection for lack of novelty is maintained by this Authority. It cannot at present be excluded that the sequences implicitly disclosed in D1/D2 do not fall within the scope of claims 10-14 (see the PCT Guidelines, Gazette PCT-Section IV, IV-7.5). The said claims are therefore not regarded as novel (Art. 33(2) PCT).

4. Inventive step (Art. 33(3) PCT):

D1-D3 are considered as the closest prior art documents.

Claim 1 is directed to a nucleic-acid based method for diagnosing asthma or a predisposition to asthma.

D1-D3 all disclose nucleic-acid based methods for diagnosing asthma or detecting a predisposition to asthma.

The problem solved by claim 1 over the cited prior art can be seen as the provision of an alternative method for predicting susceptibility to asthma (cf. description of the present application, page 10, lines 15-18).

The solution proposed in claim 1 consists in demonstrating the presence or absence of an allele which is associated with asthma, wherein the allele is situated at a locus in a region of chromosome 2 of up to 1 megabase in length, which region contains the locus D2S308.

This solution is regarded as inventive, because none of the cited prior art document suggests that this particular region could play a role in asthma. Claim 1 does therefore satisfy the requirements of Article 33 (3) PCT. It follows that claims 2-9 meet also the requirements for inventiveness.





International application No. PCT/GB99/00968

ITEM VII:

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art 1. disclosed in the documents D1/D2 are not mentioned in the description, nor are these documents identified therein.

ITEM VIII:

- Claims 1-6, 8, 10-12 and 14 broadly define the following features in terms of their 1. function:
 - (i) Claims 1-6, 8: "which method comprises demonstrating in the individual the presence or absence of an allele which is associated with asthma, wherein the allele is situated at a locus in a region of chromosome 2 of up to 1 megabase in length, which region contains the locus D2S308".
 - (ii) Claims 10-12, 14: "primers for amplification of an allele "and primers capable of hybridising under suitable stringent conditions to a region either side of a region of microsatellite repeats at D2S308"

However, the description convey the impression that these functions can only be carried out in a particular way, namely by (i) amplifying the allele D2S308*3 (see page 10, description of the present application) with the (ii) primers SEQ ID NO:1 and 2 (see pages 7 and 8, description of the present application), and no alternative means are envisaged.

It is clear that the examples of a patent application do not have to be exhaustive (Rule 5.1 v) PCT) and that the claims must be formally supported by the description of the application. However, Article 6 PCT states that the claims must be fully supported by the description, i.e the support must be both formal and technical, as indicated in the PCT Guidelines, Gazette PCT-Section IV, III-6.3. While there is certainly a formal support in the description for the said claims, it is considered that the technical support provided and which would be necessary to enable the extension of the particular teaching of the description to the whole of the field claimed is not sufficient. More specifically, it is noted that in the cited prior





International application No. PCT/GB99/00968

art, the identification of asthma-related loci has been carried out, i.e large region of genomic DNA have been identified as asthma-related. Moreover, the identification of specific genes is considered to be "a significant discovery" (see D1, page 131, 1st paragraph) by the skilled person.

Consequently, the identification of specific alleles associated with asthma does not seem to be a trivial task, even for the skilled person, even when the locus is known.

When applied to the present application, this analysis of the prior art apparently leads to the conclusion that claim 1 which claims a method for detecting every allele associated with asthma, moreover within a big region of 1 to 2 Mb flanking the locus D2S308, is not fully supported by the description, because the whole of the field claimed cannot apparently be reproduced using routine methods or experimentation, as indicated by the highly skilled person working in the field.

Consequently, the same objection arises for claims directed to primers to be used in said methods.

Hence, claims 1-6, 8, 10-12 and 14 are not supported by the description as required by Article 6 PCT.

- The relative definition of the region of claims 1 and 10 (up to 1 megabase in 2. length) leaves the reader in doubt as to the extent of protection claimed, especially in the light of the description of the present application, page 3, lines 1-4; page 4, lines 16-17. It should have been clearly indicated in the claims, as it has been done in the description, where the said region starts and finishes by giving a precise reference point (see the PCT Guidelines, PCT Gazette-Section IV, III-4.1). This defect renders the definition of the subject-matter of said claims unclear (Article 6 PCT), because the location of the allele and/or of the D2S308 locus within the 1 Mb region is/are not precisely indicated. A clarification of the claim would not appear to render the claim unwieldy.
- Claims 10 and 12 do not meet the requirements of Article 6 PCT in that the matter 3. for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem:





International application No. PCT/GB99/00968

Claim 10: "A pair of oligonucleotide primers for amplification of an allele which is associated with asthma"

Claim 12: "...capable of hybridising under suitably stringent condition to a region either side of microsatellite repeats at D2S308"

The technical features necessary for achieving this result i.e. the nucleotide sequences should be added (cf. PCT Guidelines, PCT Gazette-Section IV, III-4.7). Again, it is considered that the result to be achieved (designing the primers) does involve more than trial and error, for the same reasons as under section VIII, item 1. Additionally and as indicated in the introductory portion above, the matter for which protection is sought is not clearly defined, because the primers are defined by a reference to the sequence to be amplified which is itself not precisely delimited (see Section VIII, item 2). The intended limitations are therefore not clear from claims 10 and 12 (Art. 6 PCT and PCT Guidelines, Gazette PCT-Section IV, III-4.8a).

The wording "substantially similar sequences" used in claim 9 and 13 is vague 4. and unclear and leaves the reader in doubt as to the nucleotide sequences claimed, thereby rendering the definition of the subject-matter of said claim unclear (Article 6 PCT).

CY. VON: EPA-MUENCHEN 02





13

CLAIMS

- 1. A method for diagnosing an individual as being asthmatic, or as having a predisposition to asthma, which method comprises demonstrating in a nucleic acid sample taken from an individual the presence or absence of an allele which is associated with asthma, wherein the allele is situated at a locus in a region of chromosome 2 of up to 1 megabase in length, which region contains the locus D2S308.
- The method according to claim 1, wherein the method comprises the steps of:
 - (i) providing a suitable tissue sample from the individual;
 - (ii) preparing from the tissue sample a nucleic acid sample;
 - (iii) analysing the nucleic acid sample for the presence or absence of the allele.
- 3. The method according to claim 2, wherein prior to analysis, the locus at which the allele is situated is amplified.
- 4. The method according to claim 3, wherein the amplification is by the PCR.
- 5. The method according to any one of claims 1 to 4, wherein the locus at which the allele is situated comprises microsatellite repeats of variable lengths.
- 6. The method according to claim 5, wherein amplification is performed using a pair of primers each of which hybridizes under suitably stringent conditions to a region either side of the microsatellite repeats.
- 7. The method according to any one of claims 1 to 6, wherein the allele for identification is D2S308*3.

25-04-2000

GB 009900968







- The method according to any one of claims 3 to 7, wherein the analysis 8. is carried out by size separation of amplification products.
- The method according to claim 6, wherein the primers in the pair of 9. primers comprise the oligonucleotide sequences identified by SEQ ID NO: 1 and SEQ ID NO: 2 or substantially similar sequences.
- A pair of oligonucleotide primers for amplification of an allele which is 10. associated with asthma, which allele is situated at a locus in a region of chromosome 2 of up to 1 megabase in length, which region contains the locus D2S308.
- The pair of oligonucleotide primers according to claim 10, one of which 11. is labelled with a detectable marker.
- The pair of oligonucleotides according to claim 10 or claim 11, capable 12. of hybridising under suitably stringent conditions to a region either side of a region of microsatellite repeats at D2S308.
- The pair of oligonucleotide primers according to claim 12, comprising 13. the oligonucleotide sequences identified by SEQ ID NO: 1 and SEQ ID NO: 2 or substantially similar sequences.
- An assay kit which comprises the pair of oligonucleotide primers 14. according to any one of claims 10 to 13.



PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92his 1 and

From the INTERNATIONAL BUREAU

To:

WILKINSON, Stephen, John Stevens, Hewlett & Perkins Halton House

Administrative Instructions, Section 422)	London EC1N 2JD ROYAUME-UNI		
Date of mailing (day/month/year) 25 April 2000 (25.04.00)			
Applicant's or agent's file reference	IMPORTANT NOTIFICATION		
KP/3281 PCT			
International application No.	International filing date (day/month/year)		
PCT/GB99/00968	26 March 1999 (26.03.99)		
The following indications appeared on record concerning: the applicant			
Name and Address	State of Nationality State of Residence		
WILKINSON, Stephen, John			
Stevens, Hewlett & Perkins 1Serjeants' Inn	Telephone No. +44 171 936 2499		
Fleet Street London EC4Y 1NT	Facsimile No.		
United Kingdom	+44 171 936 2498		
·	Teleprinter No.		
2. The International Bureau hereby notifies the applicant that the the person the name X the add Name and Address WILKINSON, Stephen, John Stevens, Hewlett & Perkins Halton House 20/23 Holborn London EC1N 2JD United Kingdom 3. Further observations, if necessary:			
4. A copy of this notification has been sent to:			
X the receiving Office	the designated Offices concerned		
the International Searching Authority	X the elected Offices concerned		
X the International Preliminary Examining Authority	other:		
	Authorized officer		
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Anman QIU		
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38		

TENT COOPERATION TREAT

	E CONTENTAL PURE			
PCT	From the INTERNATIONAL BUREAU			
FC1	To:			
NOTIFICATION OF THE RECORDING OF A CHANGE (PCT Rule 92bis.1 and Administrative Instructions, Section 422)	CORNISH, Kristina Kilburn & Strode 20 Red Lion Street London WC1R 4PJ ROYAUME-UNI			
Date of mailing (day/month/year)				
31 October 2000 (31.10.00)				
Applicant's or agent's file reference KP/3281 PCT	IMPORTANT NOTIFICATION			
International application No.	International filing date (day/month/year)			
PCT/GB99/00968	26 March 1999 (26.03.99)			
The following indications appeared on record concerning:				
X the applicant the inventor	the agent the common representative			
Name and Address	State of Nationality State of Residence			
ISIS INNOVATION LIMITED 2 South Parks Road	GB GB Telephone No.			
Oxford OX1 3UB United Kingdom	Total Maria			
	Facsimile No.			
	Teleprinter No.			
2. The International Bureau hereby notifies the applicant that t	he following change has been recorded concerning:			
the person the name X the add	ress the nationality the residence			
Name and Address	State of Nationality State of Residence			
ISIS INNOVATION LIMITED Ewert House	Talankana Na			
Ewert Place	Telephone No.			
Summertown Oxford OX2 7BZ United Kingdom	Facsimile No.			
Onited Kingdoni				
	Teleprinter No.			
3. Further observations, if necessary:				
4. A copy of this notification has been sent to:				
X the receiving Office	the designated Offices concerned			
the International Searching Authority	X the elected Offices concerned			
the International Preliminary Examining Authority	other:			
	Authorized officer			
The International Bureau of WIPO 34, chemin des Colombettes	Peggy Steunenberg			
1211 Geneva 20, Switzerland				
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38			



	From the INTERNATIONAL BUREAU
PCT	To:

То:

NOTIFICATION OF THE RECORDING OF A CHANGE (PCT Rule 92bis.1 and Administrative Instructions, Section 422) Date of mailing (day/month/year) 29 September 2000 (29.09.00)	CORNISH, Kristina Kilburn & Strode 20 Red Lion Street London WC1R 4PJ ROYAUME-UNI			
Applicant's or agent's file reference KP/3281 PCT	IMPORTANT NOTIFICATION			
International application No. PCT/GB99/00968	International filing date (day/month/year) 26 March 1999 (26.03.99)			
The following indications appeared on record concerning: the applicant	X the agent the common representative			
Name and Address WILKINSON, Stephen, John Stevens, Hewlett & Perkins Halton House 20/23 Holborn	State of Nationality State of Residence Telephone No. +44 20 7404 1955			
London EC1N 2JD United Kingdom	Facsimile No. +44 20 7404 1844 Teleprinter No.			
2. The International Bureau hereby notifies the applicant that the X the person the name the add	promise promis			
Name and Address	State of Nationality State of Residence			
CORNISH, Kristina Kilburn & Strode 20 Red Lion Street London WC1R 4PJ United Kingdom	Telephone No. +44 20 7539 4200			
	Facsimile No. +44 20 7539 4299			
	Teleprinter No.			
3. Further observations, if necessary:				
4. A copy of this notification has been sent to:				
X the receiving Office	the designated Offices concerned			
the International Searching Authority	X the elected Offices concerned			
the International Preliminary Examining Authority other:				
The International Bureau of WIPO	Authorized officer			
34, chemin des Colombettes 1211 Geneva 20, Switzerland	Jean-Marie McAdams			

Facsimile No.: (41-22) 740.14.35

Telephone No.: (41-22) 338.83.38





PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

WILKINSON, Stephen, John Stevens, Hewlett & Perkins 1 St. Augustine's Place Bristol BS1 4UD ROYAUME-UNI

, tallimonative monations, desired 122,	ROYAUME-UNI		
Date of mailing (day/month/year)	7[
03 February 2000 (03.02.00)			
Applicant's or agent's file reference	IMPORTANT NOTICICATION		
KP/3281 PCT	IMPORTANT NOTIFICATION		
International application No.	International filing date (day/month/year)		
PCT/GB99/00968	26 March 1999 (26.03.99)		
The following indications appeared on record concerning:			
the applicant the inventor	X the agent the common representative		
Name and Address	State of Nationality State of Residence		
PRIVETT, Kathryn, Louise Stevens, Hewlett & Perkins 1 Serjeants' Inn Fleet Street			
1 Serjeants' Inn	Telephone No.		
Fleet Street London EC4Y 1NT	0171 936 2499		
United Kingdom	Facsimile No. 0171 936 2498		
	Teleprinter No.		
	releprinter No.		
2. The International Bureau hereby notifies the applicant that t	he following change has been recorded concerning:		
X the person	dress the nationality the residence		
Name and Address	State of Nationality State of Residence		
WILKINSON, Stephen, John Stevens, Hewlett & Perkins			
1 St. Augustine's Place Bristol BS1 4UD	Telephone No.		
Bristol BS1 4UD United Kingdom	0171 922 6007		
Omica Kingdom	Facsimile No. 0171 922 6009		
	Teleprinter No.		
	rejeptimes ivo.		
3. Further observations, if necessary:			
4. A copy of this notification has been sent to:			
X the receiving Office	the designated Offices concerned		
the International Searching Authority	X the elected Offices concerned		
X the International Preliminary Examining Authority	other:		
	A sale with all afficient		
The International Bureau of WIPO	Authorized officer		

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

S. Cruz

Telephone No.: (41-22) 338.83.38

Facsimile No.: (41-22) 740.14.35



PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents United States Patent and Trademark Office Box PCT Washington, D.C.20231 ÉTATS-UNIS D'AMÉRIQUE

Date of mailing (day/month/year)
03 December 1999 (03.12.99)

International application No.
PCT/GB99/00968

International filing date (day/month/year)
26 March 1999 (26.03.99)

Applicant

COOKSON, William, Osmond, Charles, Michael et al

1.	The designated Office is hereby notified of its election made:
	X in the demand filed with the International Preliminary Examining Authority on:
	27 October 1999 (27.10.99)
	in a notice effecting later election filed with the International Bureau on:
2.	The election X was
	was not
	made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

J.M. Vivet

Telephone No.: (41-22) 338.83.38